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DUANE MORRIS LLP
ONE LIBERTY PLACE
PHILADELPHIA, PA 19103-7396
PHONE: 215.979.1000
FAX: 215.979.1020

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PATENT

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In Re Appln. of:	Eugene Roussel	Group Art Unit:	1642
Serial No.:	09/756,978	Conf. No.:	6809
Filed:	9 January 2001	Examiner:	Misook Yu
For:	Therapeutic Modulation of the Tumor Inflammatory Response	Atty Docket No.:	E0631-00001

APPLICANT'S INTERVIEW SUMMARY

This Summary is filed to comply with the Applicant's responsibility, pursuant to 37 C.F.R. §1.133(b) to provide a complete written statement of the reasoning presented at the interview conducted on 18 May 2004 with respect to the patent application referenced above.

On 18 May 2004, Applicant Eugene Roussel and his representative, Gary D. Colby conducted a personal interview with Examiner Misook Yu and Supervisory Examiner Christina Chan at the Carlyle facility of the U.S. Patent & Trademark Office, beginning at about 10:00 a.m. The interview continued until shortly after 11:00 a.m.

Exhibits and Demonstrations

Eight sheets of exhibits were displayed by the Applicant to the Examiners during the interview. Photocopies of those eight sheets accompany this Summary. Three of those sheets (numbered 6, 7, and 8 in circles in their upper right corners) were presented as a diagram of the results presented by the Lee reference (of record). A four-page excerpt of a medical immunology textbook was left with the Examiners, including page 72 of (Parslow, 1997, "The Immune Response," In: Medical Immunology, Stites, et al., Eds., Appleton & Lange, Stamford, CT). An additional copy of that four-page

U.S. Patent Application Ser. No. 09/756,978 **ATTORNEY DOCKET NO: E0631-00001**
Summary of Personal Interview
Conducted on 18 May 2004

excerpt accompanies this Summary. No demonstrations were conducted during the interview.

Claims Discussed

Claims 1-66 and 81-83 are pending in the application. All of these claims stand rejected, based on i) 35 U.S.C. § 112 (enablement); or ii) 35 U.S.C. § 103(a) over Lee in view of Tannenbaum and/or Lanni and/or additional references. Both the 112-based rejection and the 103(a)-based rejections were discussed, so all claims were discussed.

Prior Art Discussed

The Lee reference (of record) referred to in Paper No. 27 was discussed at length. The Tannenbaum reference (of record) referred to in Paper No. 27 was discussed briefly. The Lanni reference (of record) referred to in Paper No. 27 and one or more references referred to in the 35 U.S.C. § 112 rejection in Paper No. 22 were mentioned or discussed only in passing. The four-page excerpt described above was discussed.

Proposed Amendments

The Applicant proposed no amendments to the claims or specification.

Principal Arguments Presented

Rejections Pursuant to 35 U.S.C. §103(a) (obviousness)

Claims 1, 3, 7-66, and 81-83 stand rejected pursuant to 35. U.S.C. § 103(a) as being obvious over the Lee reference, in view of one or more references by Tannenbaum, Lanni, and others. The Lee reference was considered by the Examiners and the Applicant to be the base reference, and discussion centered around what is taught in that reference.

U.S. Patent Application Ser. No. 09/756,978 **ATTORNEY DOCKET NO: E0631-00001**
Summary of Personal Interview
Conducted on 18 May 2004

The arguments regarding the Lee reference made by the Applicant during the interview can be summarized as follows.

The Examiner mischaracterizes or misunderstands the Lee reference in at least several ways.

First, the Examiner asserts that Lee's use of IFN-g, TNF, and anti-Fas antibody is relevant to the claimed methods, which are directed to inducing tumor cell death IN A HUMAN PATIENT. The Examiner refers to Figure 1C in Lee, relating to administration of these three agents to cultured RENCA tumor cells. The Examiner also refers to page 232, right column, line 5, relating to peritumoral administration of anti-Fas antibody (ONLY!) to RENCA tumors implanted into mice. The Examiner asserts that these combined teachings of Lee are relevant to locally administering IFN-g, TNF, and anti-Fas antibody to a tumor in a patient. However, this is a mischaracterization of Lee.

Lee uses IFN-g and TNF only in **in vitro** experiments in which tumor cells are cultured outside of an animal (i.e., outside of a system in which there is normally a basal level of IFN-g and TNF expression). As disclosed in Lee (see first paragraph, page 238, endogenous IFN-g production was known to be necessary to facilitate Fas-mediated tumor cell apoptosis. Lee added IFN-g and/or TNF only to tumor cells grown *in vitro* - LEE DID NOT ADMINISTER (LOCALLY OR OTHERWISE) IFN-g OR TNF TO ANY ANIMAL IN WHICH TUMOR CELLS HAD BEEN IMPLANTED. Indeed, Lee showed that IFN-g knockout mice exhibit significantly less (see Figure 7A) Fas-mediated tumor cell apoptosis. The clear implication to any skilled artisan is that normal, endogenous levels of IFN-g and TNF were considered by

Lee to be sufficient to facilitate whatever Fas-mediated apoptosis-inducing effects might be attributable to anti-Fas antibodies.

Thus, even if anti-Fas antibody were considered to be an "antigen-releasing agent" as recited in the claims, Lee does not teach co-administering anti-Fas antibody and any other compound TO AN ANIMAL. The Examiner's rejection is improper for this reason alone.

Second, the Examiner asserts that anti-Fas antibody is an "antigen-releasing agent" in the sense of the claimed invention. Evidently, the Examiner believes that administering anti-Fas antibody to an animal will result in death of at least some tumor cells and release of antigens therefrom. Even if these assertions are correct, ANTI-FAS ANTIBODY IS INOPERATIVE AS AN EMBODIMENT OF AN ANTIGEN-RELEASING AGENT IN THE CLAIMED INVENTION.

Fas is a transmembrane protein which induces a chain of events resulting in apoptosis when Fas binds with either FasL (another cell-surface protein) or with certain anti-Fas antibodies. FAS IS EXPRESSED BY LEUKOCYTES[1], including by activated T cells (i.e., which are known to be involved in type 1 inflammatory responses). If an anti-Fas antibody were administered locally to a tumor, leukocytes at the tumor site would be induced to apoptose. As explained throughout the specification, the claimed invention relates to inducing the immune system to mount a (leukocyte-mediated) anti-tumor inflammatory response. If anti-Fas antibody were used as the "antigen-releasing agent" in the claimed invention, the invention would be inoperative. The skilled artisan would understand that anti-Fas antibody cannot be used in a method in which the activity of leukocytes are required.

[1] See page 72, right column, first full paragraph of Parslow, 1997, "The Immune Response," In: Medical Immunology, Stites, et al., Eds., Appleton & Lange, Stamford, CT; copy enclosed.

Third, Lee does not even teach that anti-Fas antibodies can be used to kill tumor cells. Figure 11 of Lee discloses an experiment in which (Fas-bearing) RENCA tumor cells were implanted into mice. Open circles represent RENCA-implanted mice to which a control (i.e., non-Fas-binding) antibody was administered, and filled circles represent RENCA-implanted mice to which a Fas-binding antibody was administered. If anti-Fas antibodies exhibited tumor-killing efficacy, then a skilled artisan would expect that the RENCA-implanted mice to which the Fas-binding antibody was administered would live longer (i.e., that the tumor would be slowed). In fact, the opposite effect was achieved - mice receiving anti-Fas antibodies died SOONER than did mice that received control antibody. The only mice which appeared to benefit from anti-Fas antibody administration were mice into which had been implanted RENCA tumors that had been engineered to overexpress Fas. The Examiner's assumption that anti-Fas antibodies will exhibit antigen-releasing activity when contacted with tumors that are not engineered to overexpress Fas is not taught, suggested, or supported by the Lee reference.

In summary, Lee does not teach administering IFN-g, a second IR1-promoting agent, or a leukocyte attractant to any animal. Lee also fails to teach administering any antigen-releasing agent that would be operative in the claimed invention.

The Examiners did not accept the Applicant's representations regarding the teachings of Lee, and indicated that further consideration of Lee might be required in view of the Applicant's arguments. The Examiners represented that Lee teaches that IFN-g and TNF exhibit anti-tumor activity. However, the Applicant pointed out that

although Lee indicated that IFN-g and/or TNF are able to increase expression of Fas protein on RENCA cells in vitro (i.e., thereby more closely mimicking in a dish the conditions that occur in an animal body), there is no teaching in Lee that IFN-g and/or TNF are able to induce death of RENCA cells. The Examiners indicated that further consideration of this argument would be necessary.

Further with regard to the Lee reference, the Examiners indicated that if, as the Applicant asserted, anti-Fas antibody is a non-operative embodiment of an antigen-releasing agent, then the Lee reference might not be citable as an obviating reference, but might instead by citable as evidence that the specification does not adequately enable a skilled artisan to practice the entire genus of antigen-releasing agents recited in the claims. The Examiner asserted that if anti-Fas antibody was not an operative embodiment of such an agent, then a skilled artisan would be unable to tell which compounds would be operable.

The Applicant strongly objected, asserting that the specification (citing page 13, beginning at line 5) teaches that antigen-releasing agents that are toxic to leukocytes should not be used, and that it would be clear to a skilled artisan that anti-Fas antibody was an extremely bad choice of an antigen-releasing agent for that reason. The Applicant also pointed out that a single inoperative species (or a small number of inoperative species) will not render an entire genus inoperative, particularly where it would be obvious to a skilled artisan that a particular species is inoperative. The Examiners objected that the specification did not explicitly teach that anti-Fas antibody was an inappropriate agent, to which the Applicant responded that

i) even without taking into account its leukocyte-toxicity, anti-Fas antibody would be regarded by a skilled artisan as a very poor choice of antigen-releasing agent (i.e., it would be useful with few, if any, tumors - only tumors

engineered to overexpress Fas, according to Lee), so there was no reason to specifically disparage it in the specification and

ii) the Applicant is not required by the enablement requirement to name or predict all possible members of a genus that would be inoperative, particularly where such inoperative members would be relatively rare and clearly recognized by skilled artisans as such.

No agreement was reached on this issue. The Applicant believes that Examiners neither withdrew Lee as an allegedly obviating reference nor cited it as evidence of non-enablement in a formal rejection.

With regard to the Tannenbaum reference, the Examiners represented that Tannenbaum teaches that each of IL-12, IP-10, and Mig exhibits anti-tumor effect, and that IL-12 is considered to be a leukocyte attractant in the Applicant's specification.

The Applicant pointed out that IL-12 is disclosed to be a "second IR1-promoting agent" as recited in claim 1 (see claim 29) - and that IL-12 is not disclosed in Applicant's specification to be a leukocyte attractant. The Applicant also pointed out that Tannenbaum does not disclose administration of IP-10 or Mig in any context - Tannenbaum used anti-IP-10 antibodies and anti-Mig antibodies to attempt to inactivate those agents *in vivo*. The Applicant admitted that Tannenbaum discloses systemically administered IL-12 can lead to death of RENCA cells implanted into mice, but asserted that it does not disclose administration of any of IFN-g, IP-10, and Mig. The Examiners indicated these representations differed from their previous understanding of Tannenbaum and that further consideration of the issue by them was warranted.

The Applicant argued that there was no motivation in the references cited by Examiner Yu to combine the teachings of those references, and that there was no general knowledge in the field that would lead a skilled artisan to combine the references

selected by the Examiner. The Applicant also pointed out that because Lee did not achieve any therapeutic effect in mice with non-engineered tumors, there would be no reason for a skilled artisan to combine Lee with either of the two references cited by the Examiner. The Examiners disagreed, and this issue was not discussed at length.

Rejection Pursuant to 35 U.S.C. § 112 (enablement)

Claims 2 and 4-6 stand rejected pursuant to 35 U.S.C. § 112, first paragraph, in view the Examiner's belief the claimed methods involve use of proteases to induce death of tumor cells. The Applicant indicated that the function of a protease (i.e., one type of "antigen-releasing agent") in the rejected claims is to release one or more antigens from cells of a tumor when locally administered thereto. The claims do not recite that a protease induces tumor cell death. Instead, the claims recite a method that induces tumor cell death, the method employing a protease as an antigen-releasing agent.

Examiner Yu reiterated her belief that administration of a protease would lead to tumor growth and/or metastasis. The Applicant expressed that such effects, if they occurred, might be undesirable side effects, but that they are not relevant to the issue of whether or not the relevant claims are enabled. The Applicant reiterated that enablement inquiry is directed to whether the specification provides a skilled artisan with enough information to practice the claimed methods. The Examiner took the position that tumor growth or spread would inhibit or prevent the claimed methods from being achieved. The Applicant pointed out that methods of inducing tumor cell death were being claimed, and that it was immaterial whether some tumor cells grew or migrated.

No agreement was reached on this issue.

Separately, the Examiners raised a new potential enablement issue - whether the claims could be considered enabled in view of the absence from the specification of clinical or laboratory data. The Applicant reminded the Examiners that

this rejection had previously been made by Examiner Davis (the previous Examiner of this application) and withdrawn by Examiner Yu in view of a Declaration submitted by Dr. Roussel and argumentation to the effect that the claimed methods represented a novel and non-obvious combination of previously known agents, using only known characteristics of those agents in ways not previously contemplated by others. The Applicant's understanding is that this new enablement rejection was not formally made and that the enablement rejection previously made by Examiner Davis remained overcome.

Other Pertinent Matters Discussed

The Applicant expressed severe frustration at his perception that two Examiners (Examiners Natalie Davis and Examiner Misook Yu) had considered his application and, in his opinion, had demonstrated failure to comprehend the technology that was disclosed and claimed therein. The Applicant expressed his desire that an examiner with greater familiarity with the subject matter be assigned to examine the application, and Examiner Yu conceded that it was possible that there were other examiners in the Office who had greater familiarity with the subject matter than she.

The Applicant discussed perceived communications difficulties that had occurred during prosecution of the application, and expressed concern that i) submissions by the Applicant might not have been understood by the Examiner owing to poor comprehension of the English language and ii) that portions of writings received by the Applicant from the Examiner were difficult to understand, owing to unusual English usage.

Outcome of the Interview

The Examiners did not agree that any of the claims were in condition for allowance in their present form. The Examiners suggested that claim 1 might include

U.S. Patent Application Ser. No. 09/756,978 **ATTORNEY DOCKET NO: E0631-00001**
Summary of Personal Interview
Conducted on 18 May 2004

patentable subject matter, and that it might be considered allowable if it were amended such that the Examiner's concerns regarding enablement (in view of inclusion within the genus of "antigen-releasing agents" of the anti-Fas antibody purported by the Examiners to be such an agent, as discussed above with reference to the Lee reference).

The Examiners represented that the arguments presented during the interview would be considered further if presented formally.

The Applicant's representative indicated that further discussions with the Applicant would determine the Applicant's subsequent course of action.

This Summary is accurate to the best recollection of the undersigned Applicant's representative.

Respectfully submitted,

Eugene Roussel

21 May 2003
(Date)

By:

Gary D. Colby, Ph.D., J.D.
Registration No. 40,961
Customer No. 08933
DUANE MORRIS LLP
One Liberty Place
Philadelphia, PA 19103-7396
Telephone: 215-979-1000
Direct Dial: 215-979-1849
Facsimile: 215-979-1020
E-Mail: GDColby@DuaneMorris.com

Enclosures: Eight Sheets of Exhibits
Four-page excerpt (Parslow, 1997, "The Immune Response," In: Medical Immunology, Stites, et al., Eds., Appleton & Lange, Stamford, CT)